Coronary Artery Calcium Scores and Risk for Cardiovascular Events in Women Classified as "Low Risk" Based on Framingham Risk Score

The Multi-Ethnic Study of Atherosclerosis (MESA)

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Objective: To assess coronary artery calcium (CAC) score and subsequent risk for coronary heart disease (CHD) and cardiovascular (CVD) events among asymptomatic women judged to be at low risk by the Framingham risk score (FRS), a common approach for determining 10-year absolute risk for CHD. Based on population survey data, 95% of American women are considered at low risk based on FRS.

Methods: The Multi-Ethnic Study of Atherosclerosis (MESA) included 3601 women aged 45 to 84 years at baseline. The CAC score was measured by coronary computed tomography. Cox proportional hazard models were used to examine the CHD and CVD risk associated with CAC score among women classified as "low risk" based on FRS.

Results: Excluding women with diabetes and those older than 79 years, 90% of women in MESA (mean±SD age, 60±9 years) were classified as "low risk" based on FRS. The prevalence of CAC (CAC score >0) in this low-risk subset was 32% (n=870). Compared with women with no detectable CAC, low-risk women with a CAC score greater than 0 were at increased risk for CHD (hazard ratio, 6.5; 95% confidence interval, 2.6-16.4) and CVD events (hazard ratio, 5.2; 95% confidence interval, 2.5-10.8). In addition, advanced CAC (CAC score ≥300) was highly predictive of future CHD and CVD events compared with women with nondetectable CAC and identified a group of low-risk women with a 6.7% and 8.6% absolute CHD and CVD risk, respectively, over a 3.75-year period.

Conclusions: The presence of CAC in women considered to be at low risk based on FRS was predictive of future CHD and CVD events. Advanced CAC identified a subset of low-risk women at higher risk based on current risk stratification strategies.

Arch Intern Med. 2007;167(22):2437-2442

GLOBAL RISK ASSESSMENT BY the Framingham risk score (FRS) is a standard approach for estimating the 10-year absolute risk for coronary heart disease (CHD). In the United States, low risk is considered to be an estimated risk of less than 10% in 10 years; high risk is considered to be 20% or greater in 10 years; and intermediate risk is between these 2 extremes.[1] Data from the Third National Health and Nutrition Examination Survey (NHANES III) demonstrate that 95% of US women younger than 70 years are judged to be at low risk for CHD[2] and therefore, according to the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) (NCEP/ATP III), do not qualify for more aggressive medical management for standard risk factors.[1] Nevertheless, most women will ultimately die of heart disease, suggesting that the FRS alone does not adequately stratify women in ways that would be useful for targeted preventive interventions. Therefore, further work is needed to understand if certain groups of women, despite a low-risk designation by FRS, might actually be at greater risk of CHD and potentially merit more aggressive preventive medical therapy.

For editorial comment see page 2399

The goal of this analysis was to determine the prevalence and prognostic signifi-

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cance of subclinical coronary calcium measured by computed tomography (CT) in women from the Multi-Ethnic Study of Atherosclerosis (MESA) who were classified as "low risk" based on FRS.

METHODS

The MESA is a multiethnic longitudinal epidemiological study of 3601 women and 3213 men aged 45 to 84 years that was initiated in July 2000 to understand the importance of subclinical atherosclerosis measures as well as other factors in individuals without known cardiovascular disease (CVD).[3] This prospective cohort study includes individuals from 6 US communities (Baltimore, Maryland; Chicago, Illinois; Forsyth County, North Carolina; Los Angeles County, California; northern Manhattan, New York; and St Paul, Minnesota) and consists of 38% white, 28% African American, 22% Hispanic, and 12% Asian (of Chinese descent) subjects. For the present study, we included nondiabetic women younger than 79 years, who were classified as "low risk" (estimated risk of <10% in 10 years) by FRS, yielding 2684 women.

Medical history, anthropometric measurements, and laboratory data for the present study were taken from the first examination of the MESA cohort (July 2000 to August 2002). Information about age, sex, ethnicity, and medical history were obtained by questionnaires administered at the screening and the first examination. Diabetes was defined as a fasting glucose level of 126 mg/dL or greater (to convert to millimoles per liter, multiply by 0.0555) or use of hypoglycemic medications. Current smoking was defined as having smoked a cigarette in the last 30 days. Family history of CVD was defined in MESA as a parent, sibling, or child with history of myocardial infarction. Use of oral estrogen (including estrogen alone or in combination with progestins) and/or aspirin was derived from medication lists and was based on clinical staff entry of prescribed medications.

Resting blood pressure was measured 3 times in the seated position using a Dinamap model Pro 100 automated oscillometric sphygmomanometer (Critikon, Tampa, Florida), and the mean of the second and third readings was recorded. Hypertension was defined as a systolic blood pressure of 140 mm Hg or higher, a diastolic blood pressure of 90 mm Hg or higher, or use of medication prescribed for hypertension. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Total and high-density lipoprotein cholesterol (HDL-C) were measured from blood samples obtained after a 12-hour fast. Low-density lipoprotein cholesterol (LDL-C) was calculated with the Friedewald equation.[4]

Computed tomographic scanning of the chest was performed either with an electrocardiogram-triggered (at 80% of the RR interval) electron beam CT scanner (Chicago, Los Angeles, and New York field centers; Imatron C-150; Imatron, General Electric, Fairfield, Connecticut)[5] or with prospectively electrocardiogram-triggered scan acquisition at 50% of the RR interval with a multidetector CT system[6] that acquired 4 simultaneous 2.5-mm slices for each cardiac cycle in a sequential or axial scan mode (Baltimore, Forsyth County, and St Paul field centers; Lightspeed [General Electric] or Volume Zoom [Siemens, New York City, New York]). Each participant was scanned twice.

Scans were read centrally at the Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center to identify and quantify coronary artery calcium (CAC). The CAC scores among scanning centers and between participants were adjusted with a standard calcium phantom scanned simultaneously with each participant. The mean Agatston score was used in all analyses.[7] Agreement with regard to presence of CAC was high (κ statistic, 0.90 to 0.93 between and within readers), and the intraclass correlation coefficient for the Agatston score between readers was 0.99.[8] Agreement between scans was good for both the electron-beam CT and the multidetector CT scanner.[8] The standardized MESA methodology for the acquisition and interpretation of CAC has been previously published.[8]

DEFINITION OF CHD AND CVD EVENT

A CHD event was defined as myocardial infarction; angina, which included definite angina and probable angina if coronary revascularization was performed at the same time or afterwards; resuscitated cardiac arrest; or CHD death. A CVD event was defined as a CHD event, stroke, stroke death, other atherosclerotic death, or other CVD death.

ASCERTAINMENT OF CARDIOVASCULAR EVENT

At intervals of 9 to 12 months, a telephone interviewer contacted each participant to inquire about all interim hospital admissions, cardiovascular outpatient diagnoses, and deaths. To verify self-reported diagnoses, we requested copies of all death certificates and medical records for all hospitalizations and outpatient cardiovascular diagnoses. We also obtained next of kin interviews for out-of-hospital cardiovascular deaths. We were successful in getting hospital records for an estimated 98% of hospitalized cardiovascular events and some information on 95% of outpatient diagnostic encounters.

We abstracted hospital records suggesting possible cardiovascular events. The coordinating center collated the abstracted or original end point records and sent them to 2 paired cardiologists or cardiac epidemiologists for independent end point classification and assignment of incidence dates. If, after review and adjudication, disagreements persisted, a full mortality and morbidity review committee made the final classification.

Reviewers classified myocardial infarction as present or absent, based primarily on combinations of symptoms, electrocardiographic findings, and cardiac biomarker levels. Death from CHD was classified as present or absent based on hospital records and recorded conversations with families. Present fatal CHD required a myocardial infarction within 28 days of death, chest pain within the 72 hours before death, or a history of CHD, and required the absence of a known nonatherosclerotic or noncardiac cause of death. If the definite fatal CHD criteria were not met, possible fatal CHD could be assigned with an underlying cause of death consistent with fatal CHD and required the absence of a known nonatherosclerotic or noncardiac cause of death. Adjudicators graded angina based on their clinical judgment as absent, probable, or definite. Definite angina required clear and definite documentation of symptoms distinct from myocardial infarction diagnoses.

STATISTICAL ANALYSIS

Methods for individual Framingham 10-year CHD risk scores for each MESA woman were obtained from NCEP guidelines and calculated based on age, total cholesterol and HDL-C levels, current smoking status, systolic blood pressure, and the use of antihypertensive medication.[1] Women with diabetes (n=447), who were considered a CHD risk equivalent by NCEP/ATP III guidelines,[1] were excluded from the analysis. Individuals older than 79 years did not have a calculated FRS and were excluded. Prevalence of CAC was defined as a CAC score greater than 0. Categories of CAC score (1-99, 100-299, and $\geq$300) were also used to assess the range and severity of CAC burden.

Table 1. Baseline Characteristics of Low-Risk Women by CVD Event in MESA[a]

Characteristic	CVD Event–Yes (n=34)	CVD Event–No (n=2650)	*P* Value
Age, y	66 (7)	60 (9)	<.001
Race/ethnicity			
White	21 (62)	1086 (41)	.03
Asian (of Chinese descent)	0	314 (12)	
African American	9 (26)	714 (27)	
Hispanic	4 (12)	536 (20)	
Systolic BP, mm Hg	128±19	122±20	.06
Diastolic BP, mm Hg	70±8	69±10	.47
LDL-C, mg/dL	116±32	117±31	.77
HDL-C, mg/dL	58±14	58±15	.96
BMI	30±6	28±6	.05
Cigarette use	6 (18)	319 (12)	.06
Family history of CHD	21 (64)	1126 (45)	.03
Estrogen use	13 (38)	799 (30)	.31

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); BP, blood pressure; CHD, coronary heart disease; CVD, cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MESA, Multi-Ethnic Study of Atherosclerosis.

SI conversion factor: To convert cholesterol to millimoles per liter, multiply by 0.0259.

[a] Data are given as number (percentage) of women or mean ± SD value unless otherwise specified. Low risk = 10-year absolute CHD risk lower than 10%.

Cross tabulations were used to determine the percentage of women classified as "low risk" based on FRS with prevalent CAC (CAC score >0). Kaplan-Meier curves were constructed to illustrate the cumulative incidence of CHD and CVD events by CAC score. Cox proportional hazard models were applied to examine whether prevalent CAC or categories of CAC were associated with CHD and CVD events compared with individuals with no detectable CAC. Covariates included age, ethnicity, BMI, LDL-C level, hypertension, smoking, a family history of CHD, and use of estrogen and statin medications. A test for statistical interaction between ethnicity, prevalent CAC, and risk for CHD or CVD events was also determined. $P \leq .05$ was considered statistically significant.

RESULTS

Excluding women with diabetes, 90% of women enrolled in MESA (mean±SD age, 60±9 years) were classified as "low risk" based on FRS, yielding a total of 2684 women. Low-risk women who had a CVD event were significantly older than those who did not have a CVD event (**Table 1**). There was no statistical difference in blood pressure or cholesterol measures between the 2 groups, even after excluding individuals using blood pressure medications or statins, respectively.

In women at low risk, the prevalence of CAC (CAC score >0) was 32% (n=870). Four percent of low-risk women had a CAC score of 300 or higher (**Table 2**). Differences in CAC prevalence by ethnic group was statistically significant ($P<.001$).

Among the low-risk MESA women, 24 had CHD events over a mean follow-up period of 3.75 years, resulting in an absolute event risk of 0.9%. Similarly, there were 34

Table 2. Percentage of Women Classified as "Low Risk" Based on FRS With Prevalent CAC[a]

Race/Ethnicity	CAC Score				
	0	>0	1-99	100-299	≥300
White	694 (63)	413 (37)	255 (23)	90 (8)	68 (6)
Asian (of Chinese descent)	207 (66)	107 (34)	78 (25)	22 (7)	7 (2)
African American	513 (71)	210 (29)	145 (20)	44 (6)	21 (3)
Hispanic	400 (74)	140 (26)	111 (21)	20 (4)	9 (1)
Overall	**1814** (68)	**870** (32)	**589** (22)	**176** (6)	**105** (4)

Abbreviations: CAC, coronary artery calcium; FRS, Framingham risk score.

[a] Data are given as number (percentage) of women.

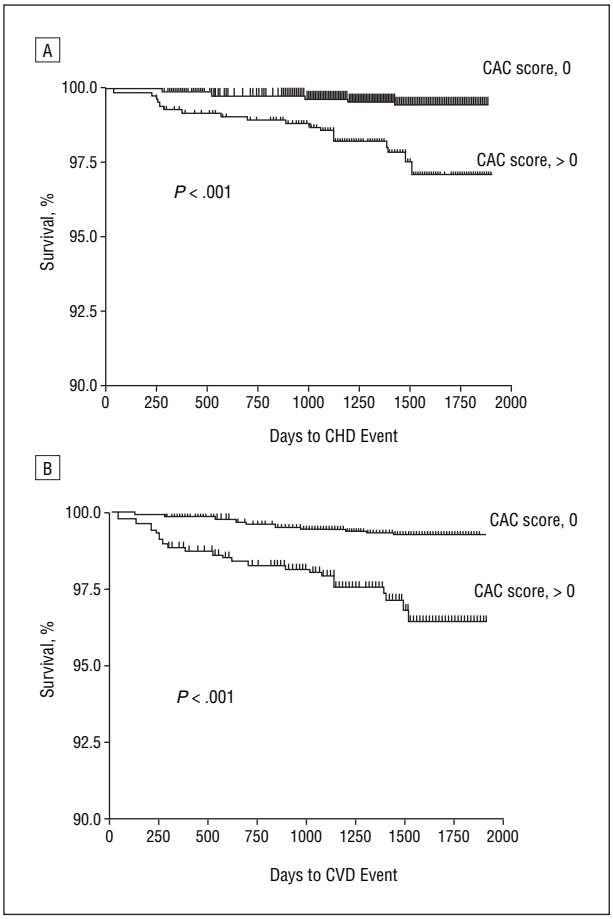

Figure 1. The cumulative incidence of coronary heart disease (CHD) (A) and cardiovascular disease (CVD) (B) events according to the presence or absence of coronary artery calcium (CAC).

CVD events in low-risk women, resulting in an overall CVD event risk of 1.3%. **Figure 1** illustrates the cumulative incidence of CHD and CVD events according to the presence or absence of CAC. There was a 6-fold greater risk for a CHD event in women with prevalent CAC compared with women with no detectable coronary calcium (hazard ratio [HR], 6.5; 95% confidence interval [CI], 2.6-16.4 [$P<.001$]) (**Table 3**). This increased risk remained significant in models adjusted for age, ethnicity, BMI, LDL-C level, hypertension, smoking, estrogen, and statin use. Similarly, there was a 5-fold greater risk of a

Table 3. Risk of CHD and CVD Events by Presence or Absence of CAC in Women Classified as "Low Risk" Based on FRS

CAC Score	No. of Events/ Total No. (%)	Unadjusted HR	*P* Value	Adjusted HR[a]	*P* Value
CHD					
0	6/1814 (0.3)	1 [Reference]		1 [Reference]	
> 0	18/870 (2.1)	6.5 (2.6-16.4)	<.001	2.8 (1.0-7.8)	.04
CVD					
0	10/1814 (0.6)	1 [Reference]		1 [Reference]	
> 0	24/870 (2.8)	5.2 (2.5-10.8)	<.001	2.3 (1.0-5.3)	.04

Abbreviations: CAC, coronary artery calcium; CHD, coronary heart disease; FRS, Framingham risk score; HR, hazard ratio.
[a]Adjusted for age, ethnicity, body mass index, low-density lipoprotein cholesterol level, hypertension, smoking, family history of CHD, estrogen use, and statin use.

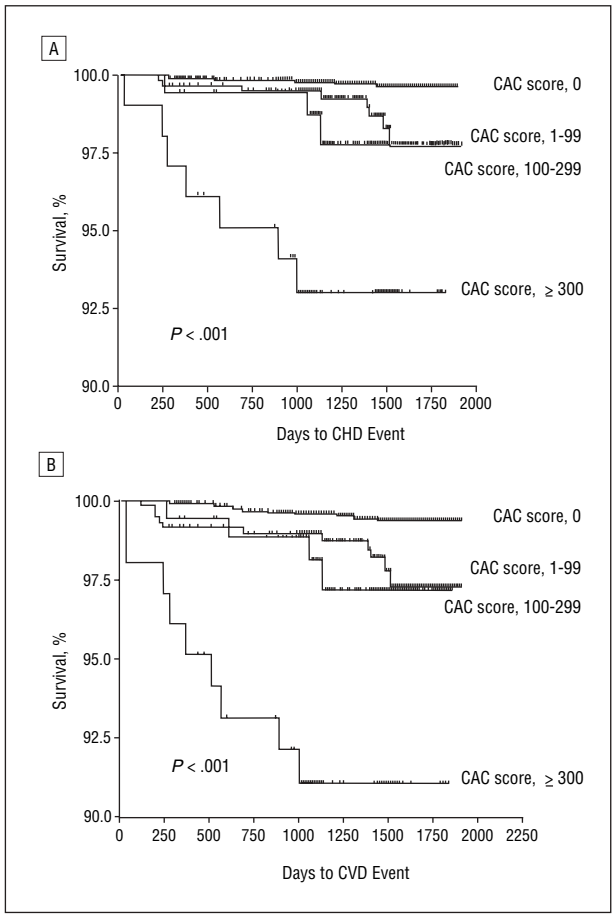

Figure 2. The coronary heart disease (CHD) (A) and cardiovascular disease (CVD) (B) event-free survival by coronary artery calcium (CAC) category in low-risk women.

CVD event in women with prevalent CAC compared with those with no detectable CAC (HR, 5.2; 95% CI, 2.5-10.8 [$P<.001$]), and this increased risk was also maintained in fully adjusted models. Models adjusted for a minimal number of covariates (age, hypertension, LDL-C level, smoking, and statin use) produced similar results (data not shown).

Figure 2 demonstrates the CHD and CVD event-free survival by CAC category in low-risk women. Increasing severity of CAC was associated with a greater relative and absolute risk for CHD and CVD events (**Table 4**). Advanced CAC (CAC score ≥300) remained associated with relative CHD and CVD risk in adjusted models and also yielded the highest absolute CHD and CVD risk over a 3.75-year period (6.7% and 8.6%, respectively).

The presence of CAC and risk for either CHD or CVD events was maintained after excluding statin users, a potentially higher-risk subset (CHD crude HR, 6.0 [95% CI, 1.9-19.1] and CVD HR, 5.5 [95% CI, 2.3-13.3], respectively). Furthermore, exclusions of both statin users and those taking antihypertensive medications produced similar CHD and CVD event estimates (CHD crude HR, 4.4 [95% CI, 1.1-19.3] and CVD HR, 4.8 [95% CI, 1.4-16.4], respectively), though the absolute number of events was small (8 CHD and 11 CVD events). For individuals with CAC scores of 300 or higher compared with those with no detectable CAC, results were similar. When assessing characteristics of women with a CAC score of 300 or higher, women were older (mean ± SD age, 69 ± 6 years), and had mean ± SD LDL-C level of 126 ± 34 mg/dL (to convert to millimoles per liter, multiply by 0.0259), and systolic blood pressure of 129 ± 20 mm Hg.

When stratifying by race, CHD event rates in women with prevalent CAC (CAC score >0) were as follows: white, 2.9% (12 of 413); Asian, 0% (0 of 107); African American, 1.4% (3 of 210); and Hispanic, 2.1% (3 of 140). In women with a CAC score of 300 or higher, 9% of whites (6 of 68), 0% of Asians (0 of 7), 5% of African Americans (1 of 21), and 0% of Hispanics (0 of 9) had a CHD event. A test for statistical interaction between ethnicity, prevalent CAC, and risk for CHD or CVD events was not significant ($P=.16$ for both).

COMMENT

The present study illustrates that roughly 30% of MESA women, classified as "low risk" by FRS, had prevalent CAC (CAC score >0) and nearly 5% had a CAC score of 300 or higher. Women with prevalent CAC had a greater risk for CHD and CVD events compared with women with no detectable CAC, although their absolute risk of events remained low. Women with advanced CAC (CAC score ≥300) had a significantly higher relative risk of CHD and CVD events than women without detectable CAC and also had an absolute CHD and CVD event risk of 6.7% and 8.6%, respectively, over a 3.75-year period.

The designation of low CHD risk (<10% risk in 10 years) by the FRS, which includes a majority of US women

Table 4. Coronary Heart Disease (CHD) and CVD Events by Coronary Artery Calcium (CAC) Score in Women Classified as "Low Risk" Based on FRS Who Were Enrolled in MESA

CAC Score	No. of Events/ Total No. (%)	Unadjusted HR	*P* Value	Adjusted HR[a]	*P* Value
CHD					
0	6/1814 (0.3)	1 [Reference]		1 [Reference]	
1-99	8/589 (1.4)	4.2 (1.5-12.0)	.008	2.4 (0.8-7.3)	.12
100-299	3/176 (1.7)	5.7 (1.4-22.9)	.01	1.5 (0.3-8.3)	.63
≥300	7/105 (6.7)	22.3 (7.5-66.5)	<.001	8.3 (2.3-30.0)	.001
CVD					
0	10/1814 (0.6)	1 [Reference]		1 [Reference]	
1-99	11/589 (1.9)	3.4 (1.5-8.1)	.005	2.0 (0.8-4.9)	.13
100-299	4/176 (2.3)	4.5 (1.4-14.3)	.01	1.4 (0.4-5.6)	.62
≥300	9/105 (8.6)	17.3 (7.0-42.5)	<.001	6.0 (2.1-17.2)	.001

Abbreviations: CVD, cardiovascular disease; FRS, Framingham risk score; HR, hazard ratio; MESA, Multi-Ethnic Study of Atherosclerosis.
[a]Adjusted for age, ethnicity, body mass index, low-density lipoprotein cholesterol level, hypertension, smoking, family history of CHD, estrogen use, and statin use.

younger than 70 years, categorizes populations of women in middle age and older adulthood over a 10-year period. An FRS designation is one of the best accepted estimates of an individual's risk based on populations, but the FRS cannot assign a precise estimate of CHD risk to the individual. Therefore, a diagnostic modality that augments traditional risk stratification to improve CHD risk assessment would potentially be useful if it were both predictive of disease and led to effective interventions that were cost-effective.

In the present study, the presence of CAC was common in low-risk women and was also highly predictive of future CHD and CVD risk. In addition, a CAC score of 300 or higher was associated with both a high relative risk and absolute CHD and CVD risk. These results are of importance because, to our knowledge, this is the first known study to focus on the predictive value of CAC in a low-risk population of women. One previous study has demonstrated an association between CAC and risk for all-cause mortality in women based on self-reported risk factors,[9] and one report has demonstrated the prognostic value of CAC in elderly women and incident myocardial infarction.[10] Future studies will be required to determine whether screening for CAC and subsequent treatment is a cost-effective strategy in this low-risk subset.

At present, high-risk individuals (estimated 10-year absolute risk of >20%) or CHD equivalent groups such as those with diabetes receive the most aggressive medical management for primary prevention. More aggressive pharmacologic treatment of an intermediate-risk group (between 10%-20% risk in 10 years) is still controversial but may be beneficial.[11] In the present study, low-risk women with advanced CAC had the highest CHD and CVD event risk compared with those women with less severe subclinical atherosclerosis, potentially identifying them as candidates for more intensive risk factor treatment. These results are consistent with a recent study demonstrating that increasing severity of CAC is associated with the highest mortality rates in a large registry of men and women.[12] Future studies will need to determine whether treating this group of women with more aggressive medical therapies will result in a reduction of CHD events over the short-term (10 years) and a lifetime.

A majority of women will die from CHD, the largest component of CVD-related deaths.[13] However, women rarely reach an intermediate- to high-risk group until the age of 70 years but have 1 major CHD risk factor (ie, hypertension, high cholesterol level, or smoking) throughout middle age. Indeed, when assessing lifetime risk in the Framingham Heart Study, a 50-year old woman with 1 major risk factor has a 50% lifetime risk with an 8-year shorter median survival (compared with women with all optimal risk factors), despite a 10-year FRS of only 2%.[14] Thus, treating 1 known risk factor aggressively in women is important in offsetting CVD burden in women, despite a low-risk FRS designation. Future studies will determine the utility of CAC scores in assessing CHD- or CVD-related events in women over a lifetime.

There are several limitations to the present study. The MESA consisted of a noninstitutionalized sample of individuals without known CVD from 6 designated US sites. While this cohort is not truly representative of the US population, it does include significant representation of 4 of the most common ethnic groups in the United States. Moreover, the percentage of age-sex stratified individuals by FRS who were enrolled in MESA are similar to the results from the NHANES data,[2] a random sample of the US population. A family history of CHD in MESA at the baseline examination was not limited to premature CHD, a stronger predictor of CHD risk. Modest effect sizes and moderate confidence intervals leave open the possibility of type II error. Owing to the lack of CHD and CVD events, we could not determine whether ethnic differences in CAC prevalence among low-risk women altered CHD or CVD outcomes.

In the present study, women classified as "low risk" based on FRS with prevalent CAC had a higher risk for future CHD or CVD events compared with low-risk women without detectable CAC. In addition, low-risk women with advanced CAC had especially high relative and absolute risks for CHD and CVD events. These data shed new light on CVD risk and the modalities to evaluate and treat middle-aged and older women. This study also provides novel data in support of the 2007 guidelines on CVD prevention in women, suggesting that

women with CAC are at potentially higher risk than an FRS classification would suggest.[15] A longer duration of follow-up will be required to understand the implications of CAC scoring and whether both screening and more aggressive pharmacologic therapy in lower-risk populations of women with evidence of subclinical atherosclerosis will reduce overall CHD and CVD burden.

Accepted for Publication: July 20, 2007.
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Financial Disclosure: None reported.
Funding/Support: This research was supported by contracts N01-HC-95159 through N01-HC-95166 and N01-HC-95169 and grant NHLBI T32 HL076132-01 from the National Heart, Lung, and Blood Institute.
Disclaimer: Dr Greenland is the editor of *Archives of Internal Medicine*. He was not involved in the editorial evaluation or decision to accept this article for publication.
Additional Contributions: We thank the other investigators, the staff, and the participants of the MESA study for their valuable contributions. A full list of participating MESA investigators and institutions can be found at http://www.mesa-nhlbi.org.

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